PSAP

PHARMACOTHERAPY SELF-ASSESSMENT PROGRAM

SEVENTH EDITION • BOOK 9

INFECTIOUS DISEASES

accp

AMERICAN COLLEGE OF CLINICAL PHARMACY

Bone and Joint Infections

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Learning Objectives

1. Evaluate the microbiologic features of osteomyelitis, septic arthritis, and prosthetic joint infections.
2. Given a patient's clinical features, distinguish between osteomyelitis and a soft tissue infection.
3. Given a patient's clinical symptoms, physical examination, microbiology, and imaging studies, design a therapeutic regimen and monitoring plan for bone and joint infections.
4. Develop a treatment plan for chronic suppressive therapy used for bone and joint infections.
5. Evaluate therapeutic regimens for bone and joint infection for potential adverse effects, and modify treatment and monitoring plans accordingly.

Introduction

Bone and joint infections include osteomyelitis, septic arthritis, and prosthetic joint infections (PJIs). These infections are difficult to treat and often require surgical management and prolonged antimicrobial therapy. Infections of the bone and joint can lead to chronic recurring infections and significant impairment to the area involved, including loss of function or mobility. Complications such as sepsis and loss of a limb are serious and may be avoided or reduced with prompt management.

Antibiotic therapy is crucial to the treatment and cure of bone and joint infections. Common antibiotics and their dosage, route of administration, and need for dosage adjustments in patients with kidney insufficiency are listed in Table 1-1.

Bone Infections

Pathophysiology

Osteomyelitis can be classified as hematogenously or contiguously spread or related to vascular insufficiency. Hematogenous osteomyelitis generally occurs in rapidly growing bone. Children are often affected with hematogenous osteomyelitis of the femur, tibia, and humerus. In older patients, hematogenous osteomyelitis usually affects the vertebrae. Contiguously spread osteomyelitis usually presents in the femur, tibia, and hip, whereas osteomyelitis caused by vascular insufficiency affects the feet and toes.

The vascular organization within the long bones predisposes them to the development of osteomyelitis. Slowing of bloodflow through the metaphyseal vascular loops allows settling of bacteria that may be present in the bloodstream. An inflammatory exudate forms within the bone, leading to pressure that can rupture the periosteum. Necrosis can result with subsequent sequestrum formation. Sequestrum is an area of devitalized bone that can act as a foreign body to which organisms can attach, leading to further bone destruction.

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Armstrong EP, Friedman AD. Bone and joint infections. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 7th ed. Boston: McGraw-Hill, 2008:1933–42.
- Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. Philadelphia: Churchill Livingstone, 2010:chaps 102–104.

Etiology

A single organism is generally responsible for hematogenous osteomyelitis, with *Staphylococcus aureus* being the most common. Hematogenous osteomyelitis affecting older patients can involve less-common bacteria such as gram-negative bacilli, anaerobes, and mycobacteria. Bacterial sources of vertebral osteomyelitis include skin and soft tissue, urinary tract, intravenous drug use, long-term intravenous catheterization, and respiratory tract. In addition to *S. aureus*, coagulase-negative staphylococci are encountered. Gram-negative bacilli and *Candida* spp. can cause vertebral osteomyelitis in intravenous drug users.

Contiguous osteomyelitis results from direct inoculation of the bone from an exogenous source or from a nearby infected focus. Soft tissue infections, trauma, open fractures, and invasive orthopedic procedures can

Table 1-1. Considerations for Common Antibiotics Used in the Treatment of Bone and Joint Infections

Drug	Dosage and Route	Laboratory Parameters	Adjustment for Kidney Impairment
Cefazolin	2 g IV q8h	CBC, BMP	Yes
Cefepime	2 g IV q8–12h	CBC, BMP	Yes
Ceftazidime	2 g IV q8–12h	CBC, BMP	Yes
Ceftriaxone	2 g IV daily	CBC, BMP	No
Ciprofloxacin	400 mg IV q8–12h 750 mg PO BID 250–500 PO BID (chronic suppression)	CBC, BMP	Yes
Clindamycin	600 mg IV q8h 300 mg PO TID (chronic suppression)	CBC, LFT	No
Co-trimoxazole	4 mg/kg per dose IV BID; 1 DS tablet PO daily (chronic suppression)	CBC, BMP	Yes
Daptomycin	6 mg/kg IV daily	CBC, BMP, CK	Yes
Doxycycline	100 mg PO BID	LFT, BMP	No
Ertapenem	1 g IV daily	CBC, BMP, LFT	Yes
Levofloxacin	750 mg IV/PO daily 250–500 mg PO daily (chronic suppression)	CBC, BMP	Yes
Linezolid	600 mg IV/PO BID	CBC	No
Meropenem	1–2 g IV q8h	CBC, BMP	Yes
Minocycline	100 mg PO BID	LFT, BMP	Yes
Moxifloxacin	400 mg IV/PO daily	CBC, BMP, LFT	No
Nafcillin	2 g IV q4h	CBC, BMP, LFT	No
Piperacillin/Tazobactam	3.375 g IV q6h	CBC, BMP	Yes
Rifampin	600 mg PO daily 300–450 mg PO BID	LFT	No
Vancomycin	15–20 mg/kg IV q8–12h	CBC, BMP, trough	Yes

BID = two times/day; BMP = basic metabolic panel; CBC = complete blood cell count; CK = creatine kinase; DS = double strength; h = hours; IV = intravenously; LFT = liver function test; PO= orally; q = every.

lead to contiguous osteomyelitis. This type of osteomyelitis is more common in patients older than 50 years. Although *S. aureus* often produces this type of infection, polymicrobial infections involving gram-negative bacilli, coagulase-negative staphylococci, and anaerobes can occur.

Patients with osteomyelitis related to vascular insufficiency typically have underlying diabetes mellitus. Neuropathy is often present in these patients, which can lead to traumatic injury and surrounding cellulitis. Wound healing is slow in patients with diabetes; this can cause skin ischemia and lead to chronic ulcers. These infections can result in contiguously spread osteomyelitis. Because of these conditions, anaerobic bacteria are common pathogens, together with *S. aureus* and gram-negative bacilli.

Chronic osteomyelitis is a recurrent infection in the same area(s) as the initial episode; sequestrum is generally the cause. This type of osteomyelitis has a very poor prognosis because treatment failure rates are high and surgical interventions are usually required. Hyperbaric oxygen is one treatment method used for chronic osteomyelitis, especially when limb salvage is attempted. Hyper-oxygenating tissue could theoretically activate neutrophils and macrophages, prevent the release of bacterial endotoxins, down-regulate cytokines, up-regulate growth factors, and potentiate antimicrobial effects. Unfortunately, hyperbaric oxygen has only theoretical benefits, and little published literature supports this treatment. Although some may find it beneficial, hyperbaric oxygen is not a generally accepted method of limb salvage. Many severe cases of chronic osteomyelitis will require amputation. Amputation is considered when adequate wound healing does not occur and all other treatment methods such as hyperbaric oxygen, aggressive wound therapy, and antimicrobial treatment are exhausted.

Diagnostic Criteria

In many cases of osteomyelitis, patients experience pain, swelling, erythema, and decreased motion of the involved area, together with constitutional symptoms such as fever, chills, and fatigue. For patients who develop osteomyelitis caused by vascular insufficiency, symptoms are less noticeable because of the effects of underlying neuropathy. Patients may have only slight local symptoms together with fever. In most cases, osteomyelitis is considered an indolent infection, with diagnosis occurring weeks to months after the initial infection. Acute osteomyelitis of the knee, hip, and shoulder can present as septic arthritis because these joints are located near the metaphysis.

Diagnosing osteomyelitis requires an evaluation of clinical signs and symptoms and a thorough assessment of radiographic and laboratory evidence. Blood cultures are generally not helpful in the diagnosis of osteomyelitis; however, patients presenting with sepsis should have two or three sets of blood cultures obtained. Hematogenous osteomyelitis indicates that the infection arose from bacteria in the bloodstream. When the patient shows septic symptoms, blood cultures can assist in diagnosis of the organism(s). Blood cultures in patients without sepsis symptoms are less likely to be positive.

Other markers that are usually recommended to evaluate osteomyelitis include white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Although these markers are relatively nonspecific, they can provide information on the degree of inflammation or infection present. It is helpful to monitor the ESR and CRP during the treatment course. If these values are elevated at baseline, it is anticipated that they will decline to close to normal range at the end of therapy. However, these values may be elevated because of other underlying inflammatory or autoimmune disease states such as systemic lupus erythematosus or rheumatoid arthritis. In this case, ESR and CRP may not be useful measurements of inflammation related to the infection.

Radiographic evidence is one of the most important tools to diagnose osteomyelitis. Often, radiography is not positive in early osteomyelitis. To visualize active osteomyelitis, much of the bone matrix must be destroyed, which generally does not occur for weeks after the osteomyelitis process begins. Many clinicians use technetium bone scans, indium-labeled WBC scans, or magnetic resonance imaging (MRI) to radiographically diagnose osteomyelitis if plain radiography is negative. In patients presenting with possible vertebral osteomyelitis, MRI is the best radiographic test. For patients with osteomyelitis of the lower extremities, MRI or nuclear imaging should be used. Although nuclear imaging is useful, a false-positive result can be produced by several factors (e.g., fracture, malignancy, recent trauma, degenerative disease, other noninfectious inflammatory process). If bone can be seen or probed on physical examination, a diagnosis of osteomyelitis is definitive, and other radiographic tests need not be obtained.

Once a diagnosis of osteomyelitis is made, it is important to identify a pathogen. Culture results must be accurate to determine appropriate treatment. Percutaneous needle aspiration can be useful when soft tissue fluid collections are present. If joint effusions are present, then joint fluid aspirations can also be used. Wound swabs are often unhelpful because many common skin pathogens colonize wounds and may be the predominant organisms on culture. The most accurate sample and gold standard for microbiologic diagnosis comes from an open biopsy or bone cultures taken during debridement.

Treatment

Successful antimicrobial therapy is crucial to treat and cure osteomyelitis. The primary goal for osteomyelitis is to preserve the normal functioning of the affected area. Acute osteomyelitis is often cured with targeted therapy that is initiated immediately after diagnosis. Chronic osteomyelitis is much more difficult to cure because infection can persist with time. Therapeutic failures are common with chronic osteomyelitis, making surgical intervention necessary in most cases.

Administration Route

Optimizing antimicrobial concentrations at the infection site is essential. Even though some antimicrobials may achieve adequate concentrations in healthy bone, limited vascular supply impedes achieving adequate concentrations in diseased bone. Of importance, therefore, vascular perfusion to the infection site should be considered. Even in healthy bone, antimicrobial concentrations are considerably lower than serum concentrations. Antimicrobials must be able to penetrate the infected tissue and exceed the minimum inhibitory concentration (MIC) of susceptible bacteria. For this reason, bactericidal antimicrobials should be used (e.g., β-lactams, fluoroquinolones, vancomycin).

For some antimicrobial agents (e.g., fluoroquinolones), serum concentrations achieved with oral administration are comparable to intravenous therapy. Oral therapy may lead to adequate serum and tissue concentrations required for cure. Oral therapy is also more convenient and often less expensive for the patient. For other antimicrobial agents (e.g., β-lactams), doses taken orally to achieve concentrations equivalent to those achieved with intravenous administration would likely not be tolerated. These agents should be administered intravenously, which requires placement of a long-term central venous catheter. However, β-lactams may be useful as chronic oral suppression after a long-term intravenous course.

Empiric Therapy

Empiric therapy for hematogenous osteomyelitis should be directed toward the most probable organism, *S. aureus.* Common antibiotic therapies for hematogenous osteomyelitis include nafcillin, oxacillin, and cefazolin for methicillin-susceptible *S. aureus* (MSSA) and vancomycin for methicillin-resistant *S. aureus* (MRSA). In addition to gram-positive coverage, intravenous drug users should receive gram-negative coverage such as an extended-spectrum penicillin, cephalosporin, carbapenem, or fluoroquinolone.

If bone cultures cannot be obtained or if cultures are pending, empiric therapy should be employed with the assumption of a polymicrobial infection. This is generally true with osteomyelitis in patients with vascular insufficiency or diabetes mellitus. *S. aureus* is a common pathogen associated with this type of osteomyelitis.

Gram-negative enteric bacilli and anaerobic organisms are also commonly isolated. Anaerobic flora does not grow well on culture, so therapy against anaerobes should be provided, especially in the presence of necrotic tissue and/or foul-smelling, purulent drainage from the infection site. Clindamycin and metronidazole may be used for anti-anaerobic coverage; however, certain β-lactams offer exceptional anaerobic activity, making it easier to use one drug for polymicrobial conditions. These agents include carbapenems and β-lactam/β-lactamase inhibitor combinations. Empiric therapy could also consist of third- or fourth-generation cephalosporins with either clindamycin or metronidazole. Vancomycin therapy should also be provided if the patient has known colonization with MRSA or has other health care–associated risk factors (e.g., recent hospitalization, antibiotic use within the last 90 days, hemodialysis, residence in a nursing home).

Targeted Therapy

Methicillin-resistant *S. aureus,* including community-associated strains, is becoming the predominant pathogen encountered with all types of osteomyelitis. For MSSA, penicillinase-resistant penicillins (e.g., nafcillin, oxacillin) are generally recommended as first-line treatment. Cefazolin, a first-generation cephalosporin, is also appropriate for the treatment of MSSA osteomyelitis. Cefazolin allows easier administration (i.e., every 8 hours in patients with normal kidney function) and a very favorable adverse effect profile. Third- and fourth-generation cephalosporins have been used to treat MSSA infections; however, MICs are higher than that for cefazolin. These agents have gram-negative activity that may be unnecessary when *S. aureus* is the causative pathogen.

Fluoroquinolones such as levofloxacin and moxifloxacin have activity for *S. aureus*; however, resistance can develop quickly. Although these agents are not generally recommended as first-line therapy, they may offer a useful oral option, especially in patients who require chronic suppressive therapy. Use of vancomycin for MSSA osteomyelitis should be reserved for patients who are intolerant of β-lactams because the relapse rate is higher when vancomycin is used versus a β-lactam antibiotic.

For osteomyelitis caused by MRSA, several treatment options are available. Vancomycin remains the drug of choice for osteomyelitis caused by MRSA despite high failure and recurrence rates. Studies using rifampin as adjunctive therapy to a second agent have had varied outcomes. In studies, adding rifampin to a β-lactam or vancomycin yields better clinical outcomes than does either agent alone, especially for bone and hardware infections. The Infectious Diseases Society of America (IDSA) clinical practice guidelines for the treatment of MRSA recommend vancomycin as first-line therapy,

adding rifampin for patients with MRSA bacteremia and osteomyelitis.

According to IDSA guidelines, vancomycin trough concentrations should be 15–20 mcg/mL throughout therapy. Traditionally, vancomycin trough concentrations between 10 mcg/mL and 20 mcg/mL were considered therapeutic. Vancomycin MICs have been used as a marker for clinical failure, especially for MRSA bacteremia and pneumonia. In MRSA infections, vancomycin MICs of greater than 1 mcg/mL have been associated with treatment failure. The IDSA guidelines for the treatment of MRSA recommend higher trough concentrations to potentially improve patient outcomes. However, limited clinical data support this higher trough concentration range.

Higher trough concentrations have not been proved to improve clinical outcomes, and may carry an increased risk of nephrotoxicity. Therefore, it is essential to monitor kidney function closely when using vancomycin for bone and joint infections. Complete blood cell counts should also be monitored because vancomycin can cause hematologic abnormalities such as thrombocytopenia and neutropenia.

Daptomycin, a bactericidal lipopeptide antibiotic, is a beneficial alternative to vancomycin therapy. Daptomycin has a U.S. Food and Drug Administration (FDA)–approved labeled indication for the treatment of complicated skin and soft tissue infections. No controlled clinical trials of daptomycin for the treatment of osteomyelitis have been completed; however, case reports of daptomycin used for MRSA osteomyelitis showed excellent clinical improvement at dosages of at least 6 mg/kg/day. A drawback associated with daptomycin therapy is failures caused by the emergence of nonsusceptible isolates during therapy. Patients receiving daptomycin should be monitored for myalgias. Creatine kinase concentrations should be monitored weekly throughout therapy. The risk of myopathies increases when daptomycin is used with other drugs that can elevate creatine kinase concentrations; attempts should be made to discontinue these agents if creatine kinase becomes elevated during daptomycin therapy. If no drug-drug interactions exist, a change in therapy may be warranted, especially if the patient has symptomatic myopathy.

Telavancin, a relatively new agent closely related to vancomycin, is a lipoglycopeptide with a labeled indication for complicated skin and soft tissue infections. Advantages of telavancin include activity against vancomycin-intermediate staphylococci, no need for therapeutic drug monitoring, and decreased potential for the development of resistant organisms. Telavancin has been studied only in animal models of osteomyelitis, but it could be used as an alternative treatment for highly suspected or documented multidrug-resistant *S. aureus* osteomyelitis. One disadvantage of telavancin is its higher rate of nephrotoxicity compared with vancomycin. Patients receiving telavancin should have kidney function monitored weekly. Patients should also be counseled regarding gastrointestinal distress because this is a common adverse effect of telavancin.

Ceftaroline is an advanced-generation cephalosporin that recently received label approval for complicated skin and soft tissue infections. Ceftaroline is active against MSSA, MRSA, and vancomycin-intermediate staphylococci; vancomycin-resistant staphylococci; and daptomycin-nonsusceptible staphylococci. In addition, ceftaroline is active against some enteric gram-negative pathogens with the exception of extended-spectrum β-lactamase–producing strains and most nonfermentative gram-negative organisms (e.g., *Pseudomonas aeruginosa, Acinetobacter baumannii*). Ceftaroline has limited activity against anaerobic organisms. This drug has efficacy in experimental models of osteomyelitis; however, no human studies have been done. Ceftaroline has an excellent safety profile and may offer another option for polymicrobial osteomyelitis when cultures show susceptible organisms.

Coagulase-negative staphylococci are not as virulent as *S. aureus*; however, close to 90% of coagulase-negative staphylococci are methicillin-resistant. Treatment options for both methicillin-susceptible and methicillin-resistant coagulase-negative staphylococci are the same as for MSSA and MRSA, respectively.

Oral antimicrobial therapy has been well studied for use in children. In adults, however, data are lacking for treating osteomyelitis with oral therapy for the treatment duration. Oral options for the primary treatment of osteomyelitis caused by MSSA or MRSA are co-trimoxazole, clindamycin, doxycycline, minocycline, and linezolid, with or without rifampin. Step-down therapy after an initial treatment course with parenteral antibiotics could also be continued with these same agents.

Linezolid has been used for staphylococcal and vancomycin-resistant enterococcal osteomyelitis; however, the toxicity profile, together with serious drug-drug interactions, makes it less desirable for long-term therapy. Hematologic abnormalities (especially thrombocytopenia) and optic and peripheral neuropathy can occur with therapy that exceeds 2 weeks. Caution and close monitoring should be used when prescribing linezolid for longer periods. In addition, linezolid is contraindicated in patients with concomitant use of serotonergic agents (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin agonists, meperidine) because of the risk of serotonin syndrome.

Osteomyelitis caused by gram-negative bacteria should be treated with antibiotics to which the organism is susceptible. Broad-spectrum β-lactams and fluoroquinolones offer the best treatment because of adequate bone penetration. Among the fluoroquinolones, ciprofloxacin and levofloxacin have the best activity against gram-negative organisms and are excellent for oral

therapy. Metronidazole and clindamycin are options for infections with anaerobes; when given orally, they provide excellent serum and tissue concentrations.

Chronic Suppression

Chronic suppressive therapy has not been well studied for the treatment of chronic osteomyelitis. Most data are related to suppressive therapies for joint infections. Some clinicians advocate treating persistent cases of osteomyelitis with intravenous antibiotics for several weeks, followed by suppressive oral therapy for 1–3 months or perhaps longer. Antibiotics that can be used include fluoroquinolones, doxycycline, minocycline, co-trimoxazole, and clindamycin, with or without rifampin. Because of the rapid development of resistance with *S. aureus*, rifampin should not be used alone.

Chronic suppressive therapy may have a role in situations in which debridement cannot be performed. This type of therapy may enable the patient to maintain function and mobility while avoiding surgical intervention. However, suppressive antibiotic therapy has the downside of cost, adverse effects, and the potential for the development of resistance. Dosages of drugs commonly used for chronic suppression are shown in Table 1-1.

Therapy Duration

Therapy duration for osteomyelitis is difficult to characterize. No well-controlled studies have been done for the treatment of the many types of osteomyelitis that can occur. In addition, no guidelines exist that outline treatment courses for most cases of osteomyelitis. The IDSA clinical practice guidelines for the treatment of MRSA recommend at least 8 weeks of antibiotics, followed by 1–3 months of oral therapy for osteomyelitis caused by this pathogen.

In general, antibiotic therapy accompanies surgical intervention. Intravenous antibiotic therapy may last for 4–12 weeks depending on the treatment response. For some infections, healing can occur with the use of long-term intravenous therapy, but extended therapy with oral antibiotics for suppression may be required. Repeat imaging may be needed at the end of an extended antibiotic course to determine whether radiographic improvement has occurred. Chronic osteomyelitis is one of the most difficult types of osteomyelitis to treat. Many patients undergo several long-term courses of intravenous antibiotic therapy together with several attempts at surgical debridement. Chronic suppressive therapy may be the only option for these patients.

JOINT INFECTIONS

Septic Arthritis
Pathophysiology

Acute bacterial septic arthritis is a severe infection of a native joint that can cause destruction and loss of function. Bacteria gain access to the joint space by hematogenous spread, trauma, direct inoculation (e.g., intraarticular injection), or contiguous spread from a nearby, localized infection within soft tissue or bone. An important predisposing factor is underlying chronic inflammation, as seen in rheumatoid arthritis. Other risk factors include diabetes mellitus, corticosteroid use, chronic kidney or liver disease, and immunosuppression. The host response to acute bacterial septic arthritis produces much of the destruction to the joint space. The influx of inflammatory cells causes a purulent effusion, possibly leading to cartilage destruction and increased joint pressure.

Etiology

S. aureus is the most common cause of nongonococcal septic arthritis, accounting for more than 40% of all cases. The next most common are streptococcal infections (more than 30% of cases) and gram-negative organisms (about 20% of cases). *Escherichia coli* is the most common gram-negative organism. Other organisms such as *Haemophilus influenzae, P. aeruginosa,* and *Listeria monocytogenes* can also play a role in septic arthritis but are much less common.

Gonococcal arthritis was a common cause of septic arthritis in the 1970s and 1980s and occurred mainly in young, sexually active adults, but the incidence has declined greatly. Seen most often in adults younger than 30 years, it is more likely to occur in women than in men. Gonococcal arthritis occurs secondarily to bacteremia caused by a mucosal infection with *Neisseria gonorrhoeae* in the urethra, cervix, rectum, or oropharynx. Disseminated gonococcal infection is the bacteremic form, usually accompanied by fevers, chills or rigors, polyarthralgia, and skin lesions or rash.

Diagnostic Criteria

Significant tenderness, swelling, erythema, fever, chills, and decreased motion of the affected joint(s) accompany bacterial septic arthritis. Monoarthritis is more common than polyarthritis. Nongonococcal arthritis is generally monoarticular, the knee being the most commonly infected joint. Polyarticular septic arthritis can be seen in patients with underlying immunosuppression or rheumatoid arthritis or in severe and extended bacteremia caused by *S. aureus.*

Disseminated gonococcal infection can present as a polyarthritis. The knees, ankles, and wrists are common joints affected with gonococcal arthritis. Patients can also present with mucosal gonococcal infection and should have cultures obtained from these sites.

Acute bacterial septic arthritis is generally associated with elevated ESR, CRP, and WBC. Immediate joint aspiration with synovial fluid analysis is extremely important. The WBC in infected synovial fluid is usually 50×10^3 cells/mm^3 to 200×10^3 cells/mm^3. Blood

cultures are also valuable because they are positive in about 50% to 70% of nongonococcal arthritis cases.

A Gram stain of synovial fluid can assist in early identification of the infecting pathogen and should be performed. Synovial fluid cultures are extremely useful. These cultures are usually positive for the causative pathogen(s), especially in nongonococcal arthritis. Plain film radiography often shows joint capsule distention and swelling of the soft tissue. Computerized tomography and MRI may help evaluate erosive bone changes and cartilage destruction.

Treatment

Treatment goals include promptly decreasing inflammation and preserving joint function. Joint drainage by closed-needle aspiration is recommended for infected joints, except for the hip, which usually requires open drainage and irrigation. Joint aspirations may be repeated several times until effusions are no longer present. Arthroscopy is also an important modality that allows irrigation of the joint.

Antimicrobial therapy for septic arthritis should be guided by Gram stain and culture. For MSSA, intravenous penicillinase-resistant penicillins (e.g., nafcillin, oxacillin) are considered first-line therapy, followed by cefazolin. Vancomycin should be used for MRSA. Daptomycin and linezolid are considered alternatives to vancomycin; however, published data are lacking. These agents should be considered in patients who are intolerant to vancomycin or whose infection has not responded appropriately to vancomycin after several days of therapy.

Despite the lack of clinical evidence with daptomycin and linezolid, these agents have benefits. Daptomycin is a once-daily intravenous antibiotic that allows easier administration in the community setting. Linezolid offers a potential alternative given its oral formulation, but it has significant toxicity with prolonged therapy and potentially serious drug-drug interactions. Therapy duration for nongonococcal septic arthritis is between 2 weeks and 4 weeks. For *S. aureus* septic arthritis, therapy should continue for 3–4 weeks and longer if osteomyelitis is present.

Empiric therapy for suspected gram-negative infections of the joint should be broad to cover organisms such as *P. aeruginosa,* which are more resistant, until final cultures and susceptibilities are known. When culture and susceptibility data become available, therapy should be tailored to the most cost-effective agent with the narrowest spectrum. In general, intravenous penicillins, cephalosporins, carbapenems, and oral fluoroquinolones offer excellent treatment options for gram-negative pathogens. Therapy for gram-negative organisms should continue for 2–4 weeks.

Gonococcal arthritis is treated with ceftriaxone 1 g intravenously daily or cefotaxime 1 g intravenously every 8 hours. If the response is adequate and the organism is susceptible, therapy can be changed to oral cefixime or cefpodoxime for 7–10 days. Doxycycline is an acceptable alternative for patients with serious β-lactam allergies. Fluoroquinolones also offer a simple treatment option; however, *N. gonorrhoeae* resistance is increasing throughout the United States. If a sensitive organism has been isolated, a fluoroquinolone is a possible alternative to ceftriaxone. For disseminated gonococcal infection, patients usually require hospitalization and prompt treatment with intravenous ceftriaxone or cefotaxime. Depending on the severity of illness, patients with the disseminated form may require longer therapy.

Prosthetic Joint Infections
Pathophysiology

Prosthetic joint infections are an extremely unfortunate complication for procedures that would normally lead to improved mobility and function in patients who were otherwise debilitated. Many infections require removal of the prosthesis, which can lead to worse functional impairment than existed before the procedure.

Prosthetic joints act as foreign bodies, allowing organisms to adhere to and to become sequestered on their surfaces, thereby preventing host defense mechanisms from eradicating the infection. Organisms that live within biofilm often cause infections. Biofilm is a polymeric matrix that often forms on foreign bodies and creates an environment resistant to host-killing mechanisms. Organisms within the biofilm layer often reach a stationary growth phase, allowing them to live longer.

Etiology

Prosthetic joints become infected by either contiguous or hematogenous spread. A contiguous PJI is generally caused by a wound adjacent to the surgical site or direct inoculation at the time of surgery. Deep-seated infections, such as suture abscesses, can also be seen. Risk factors for PJI development include surgical site infections, underlying malignancy, prior joint arthroplasty or surgery, immunosuppression, poor nutritional status, diabetes mellitus, and rheumatoid arthritis.

The most predominant organism encountered in PJIs is *S. aureus*. Coagulase-negative staphylococci are also very common. Gram-negative bacilli account for about 25% of PJIs. In addition, streptococci and anaerobic organisms can be responsible.

Diagnostic Criteria

The principal signs of PJIs are progressive joint pain and immobility together with swelling, erythema, and possibly fever. *S. aureus* is a particularly virulent pathogen that can lead to a fulminant sepsis syndrome. However, coagulase-negative staphylococci are generally associated with an indolent infection.

Radiography, including nuclear scans, has a relatively low sensitivity and specificity for diagnosis of active infection. Joint fluid analysis, in addition to radiography, is recommended. Joint fluid leukocyte counts of more than 1000 cells/mm^3 with a high percentage of neutrophils (more than 60%) indicate an active infection. Elevated peripheral WBC, ESR, and CRP are also helpful in validating a diagnosis of PJI.

Operative cultures are required to diagnose PJI definitively. Several cultures should be taken of fluid and tissue at the time of surgery; if all are positive, this indicates an increased probability of infection. Intraoperative cultures assist in determining the precise cause of the PJI, allowing appropriate antimicrobial therapy to be chosen.

Treatment

The overall therapy goal for PJIs is to prevent further loss of joint function and preserve mobility. Prosthesis revision is a common approach for PJIs. Revisions can be done in either a single- or two-stage procedure. Single-stage procedures include removal of the prosthesis, joint irrigation and debridement of infected tissue, and reimplantation with a new prosthesis together with antibiotic-impregnated cement. Single-stage procedures are associated with decreased duration of immobility, decreased cost, and lower morbidity. Successful single-stage procedures are generally performed in patients who have otherwise good health, an MSSA or streptococcal infection, and an organism that is susceptible to the antibiotic within the cement.

Two-stage procedures involve removing the infected prosthesis, joint irrigation and debridement, placement of an antibiotic-impregnated spacer, and closure of the site. Patients then receive a lengthy course of intravenous antibiotics with subsequent replacement of a new prosthesis and removal of the spacer. Cultures are often obtained during the second stage to confirm that the joint is no longer infected. Two-stage procedures are thought to have a higher success rate because the patient can obtain targeted antimicrobial therapy after spacer placement and before insertion of a new prosthesis. For total hip arthroplasty, one-stage procedures are successful about 85% of the time, whereas two-stage procedures are successful more than 90% of the time. For total knee arthroplasty, two-stage procedures are more likely used and have success rates of up to 100%.

Some clinicians advocate a more conservative approach with debridement and retention of the infected prosthesis. This procedure carries a much greater risk of reinfection. These patients also require long-term intravenous antibiotic therapy with suppressive therapy. For total hip arthroplasty, this practice is more successful for elderly patients who have a stable prosthesis, have had symptoms for less than 30 days, and do not have a gram-negative infection. Patients with an infected total knee arthroplasty who have had less than 7 days of clinical symptoms, stable prosthesis, and no signs of osteitis are more likely to have success with prosthesis retention than patients who present with more complicated infections of longer duration.

Antimicrobial therapy is a mainstay for the successful treatment of PJI. Adequate concentrations within the joint space are difficult to obtain. Not only are biofilms an obstacle, but prosthetic material lacks circulation, which is essential for antibiotic delivery to the infection site. Rifampin has the ability to penetrate biofilms, allowing improved eradication of infecting organisms. When combined with another antibiotic, rifampin effectively treats PJIs caused by staphylococci.

Nafcillin and oxacillin are considered first-line treatment of PJIs associated with MSSA. Cefazolin may be considered because of its safety profile and ease of administration. Vancomycin should be used for MRSA or MSSA when intolerances or allergies to β-lactams exist. Daptomycin is an appropriate alternative for MRSA in patients unable to tolerate vancomycin. β-Lactams and fluoroquinolones can be used for susceptible gram-negative organisms.

Duration of intravenous antibiotic therapy is generally 6 weeks with one- or two-stage procedures followed by 3 months of oral suppressive therapy for total hip arthroplasty and 6 months for total knee arthroplasty. For patients who qualify for retention of the infected prosthesis, it is recommended that intravenous antibiotics be given for 2–4 weeks followed by oral suppressive therapy. Oral suppressive therapy should be chosen on the basis of culture and susceptibility data.

Co-trimoxazole, doxycycline, clindamycin, and fluoroquinolones are commonly used for suppression after the completion of an intravenous course. Doxycycline has the advantage of a low toxicity rate. Photosensitivity can be a serious adverse effect; however, with proper precautions, doxycycline can be safe for long-term use. For both MRSA and MSSA, it is recommended to add rifampin in combination with another antistaphylococcal agent because of the presence of either prosthetic material or a spacer. In patients with a retained prosthesis, rifampin increases cure rates when used with other agents. Because of the potential of rifampin to induce the metabolism of other drugs, concomitant drugs should be evaluated and adjusted appropriately.

ROLE OF THE PHARMACIST

Outpatient Parenteral Antibiotic Therapy

When possible, it is safer and less costly to administer antibiotics orally. For some infections (e.g., osteomyelitis, joint infections), intravenous therapy may be the only option. Outpatient parenteral antibiotic therapy (OPAT) is an important advance in long-term administration. Administering intravenous antibiotics in the

home setting is a burgeoning business. Clear guidelines for OPAT are established; if these are followed, OPAT can avoid the high costs and potential health care–associated infections related to inpatient therapy. Box 1-1 lists the patient requirements to participate in OPAT.

Several antimicrobial drugs are ideal for OPAT. In general, antibiotics with long half-lives, extended shelf lives, and easy administration techniques (e.g., less-frequent dosing, intravenous push, continuous infusion) are chosen. Pharmacists can take on several roles in OPAT. Pharmacists are often responsible for procuring and dispensing the chosen antimicrobials. Pharmacists can counsel and educate the patient about the drug and the adverse reactions that may be expected. They may also monitor laboratory parameters, evaluate drug-drug interactions, and answer questions from the patient.

In some institutions, pharmacists may assume a larger role by assisting the physician with proper antibiotic choice, dosage, and duration, given the diagnosis. They may also coordinate the patient's care upon discharge and follow-up at the end of therapy. Therapy for patients enrolled in OPAT programs should be chosen on the basis of the infecting organism. It is important not only to choose the most appropriate agent but also to consider the ease of administration. For example, although nafcillin is the drug of choice for MSSA, it can often be cumbersome when given by intermittent infusions. Cefazolin may be preferred in this case because it can be given by intravenous push and has a less-frequent dosing schedule. Some home infusion agencies may be able to provide nafcillin in a pump, allowing the patient more freedom. The pump automatically administers a dose at a specific interval. In addition, a pump can provide continuous infusion of β-lactams, particularly nafcillin. In either case, the patient is required to change the drug cartridge only once daily.

Patient education is a very important part of OPAT programs. Patients and their caregivers are required to take an active role in therapy. Demonstrations on how to use the OPAT equipment and counseling for what to expect from therapy, including possible adverse effects and proper care of catheters, are common educational points for patients. Patients should be given educational materials explaining OPAT and telephone numbers for emergency contact.

Monitoring Plans

Patients being treated for bone and joint infections with long-term intravenous antibiotics require routine monitoring of not only antimicrobial therapy but also clinical response. Laboratory parameters that should be evaluated weekly are listed in Table 1-1. For some patients, wound care may be necessary to assist in proper healing. Wound care specialists can also inform the provider about the clinical response of the infection site.

Reimaging of the affected area toward the end of the treatment course can be helpful to ascertain whether the osteomyelitis is resolving from a radiographic standpoint. For patients who experience adverse reactions to the antimicrobial drug(s), discontinuing the offending agent and starting an antibiotic from a different class should be considered, depending on the adverse reaction.

Conclusion

Bone and joint infections are serious conditions with the potential to cause significant morbidity. Treatment of bone and joint infections generally requires extended courses of antibiotics. In many cases of PJIs and chronic osteomyelitis, it is difficult to eradicate the infecting pathogen, making surgical interventions a necessity. Chronic suppressive antibiotic therapy is a modality often employed for the treatment of chronic osteomyelitis. This type of therapy requires more investigation because very limited data exist to support it. For many patients receiving long-term antibiotic therapy for bone and joint infections, OPAT is an excellent way to provide therapy in a more comfortable environment.

Annotated Bibliography

1. Fraimow HS. Systemic antimicrobial therapy in osteomyelitis. Semin Plast Surg 2009;23:90–9.

    The author discusses the general principles of antimicrobial therapy for the treatment of osteomyelitis. Animal and human studies are reviewed, together with treatment recommendations for not only specific pathogens but also atypical pathogens such as vancomycin-resistant enterococci, anaerobes, and mycobacteria. The author includes a useful table showing the most common antimicrobials used for the treatment of osteomyelitis. Included in this table are the drug

name, classification, and usual dosage for osteomyelitis. In addition, the author includes a table that lists treatment options for *S. aureus,* MRSA osteomyelitis, and the evidence for effectiveness, whether in animal studies, case reports, case series, or clinical trials. The author also discusses rifampin use in combination with other agents for device-associated infections. This is a good review article for practitioners who want to understand the basic concepts of antimicrobial therapy for osteomyelitis.

2. Boffi El Amari E, Vuagnat A, Stern R, Assal M, Denormandie P, Hoffmeyer P, et al. High versus standard dose vancomycin for osteomyelitis. Scand J Infect Dis 2004;36:712–7.

Despite its retrospective nature and publication year, this study suggests that high-dose vancomycin given by continuous infusion offers better clinical outcomes for osteomyelitis without compromising renal function. This study compared high-dose vancomycin, 40 mg/kg/day, to achieve trough concentrations of 20–25 mg/L, with standard-dose vancomycin, 20 mg/kg/day, to achieve trough concentrations of 10–15 mg/L for osteomyelitis treatment. This is one of the only studies to specifically evaluate osteomyelitis and compare higher vancomycin trough concentrations with lower trough concentrations. In addition, the investigators compared intermittent vancomycin infusions with continuous infusions in the high-dose group. All patients in this study had bone biopsy–proven osteomyelitis with surgical management. The study collected and presented treatment failure, relapse, and safety data for 89 patients who received vancomycin. Twenty-one patients in the high-dose group received intermittent infusions, whereas 23 received continuous infusions. The study pooled all patients in a Kaplan-Meier analysis. In this analysis, fewer patients in the continuous-infusion high-dose group had treatment failure and kidney toxicity than in the other groups (p=0.02). Kidney failure was significantly more common in the intermittent high-dose group than in the standard-dose group (9% vs. 4.5%; p=0.0003). No patients in the continuous-infusion high-dose group had kidney failure. Mean serum trough concentrations in the standard-dose group were 10 ± 5.3 mg/dL and in the high-dose group, 24.4 ± 7.8.

3. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:1–38.

This article is the first guideline published by the IDSA for the treatment of MRSA. This reference is important for any practitioner who manages MRSA infections. Vancomycin therapy is discussed in detail. For MRSA-related osteomyelitis, the guidelines recommend surgical management followed by a long-term course of vancomycin. Daptomycin (6 mg/kg/day) is recommended as an appropriate alternative to vancomycin. The IDSA recommends the use of rifampin in

conjunction with another agent having a strength of B-III, which means that this recommendation is mainly based on expert opinions and not necessarily on published clinical trial data. For MRSA-related bone and joint infections, the IDSA recommends at least 8 weeks of antibiotic therapy with an additional 1–3 months of chronic suppressive therapy. Vancomycin trough levels should be kept between 15 mcg/mL and 20 mcg/mL for bone and joint infections, according to the guideline.

4. Edmonds M. The treatment of diabetic foot infections: focus on ertapenem. Vasc Health Risk Manag 2009;5:949–63.

The author outlines the clinical presentation, microbiology, and treatment of diabetic foot infections, focusing on ertapenem. The more common antibiotics used for treating diabetic foot infections are reviewed. In addition, the author discusses common organisms encountered in diabetic foot infections including staphylococci, streptococci, enterococci, anaerobes, Enterobacteriaceae, *Pseudomonas* spp., and *Stenotrophomonas maltophilia.* The study reviews complications such as osteomyelitis. Osteomyelitis treatment should consist of antimicrobial therapy directed at organisms cultured from bone biopsy. If using oral antibiotics, the author recommends a 12-week course. The author suggests a 4- to 6-week course if using parenteral therapy. The article discusses in detail several antibiotic classes, with ertapenem therapy highlighted. This review discusses the SIDESTEP (ertapenem versus piperacillin/ tazobactam for diabetic foot infections) trial, which evaluated outcomes of diabetic foot infection treated with ertapenem versus piperacillin/tazobactam. In the SIDESTEP study, ertapenem was non-inferior to piperacillin/tazobactam for the treatment of diabetic foot infections. The author also reviews the economic analyses of using ertapenem versus piperacillin/tazobactam. Ertapenem is associated with lower drug acquisition costs and less time and labor related to administration. This study concludes that ertapenem is a more economical choice than piperacillin/tazobactam for the treatment of diabetic foot infections. The main advantage of ertapenem over piperacillin/tazobactam is its less-frequent administration. Ertapenem is given once daily, whereas piperacillin/tazobactam is given more often. Ertapenem provides an easier treatment option than piperacillin/tazobactam for patients treated with OPAT. Given that outcomes are comparable and that ertapenem offers administration advantages, ertapenem may be considered a first-line agent for the treatment of osteomyelitis secondary to polymicrobial diabetic foot infections.

5. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885–910.

This guideline, developed by the IDSA, establishes the framework for treating diabetic foot infections. The objectives of the guideline are to reduce the burden caused by improper treatment practices and to

reduce the need for lower extremity amputation. The authors discuss osteomyelitis throughout the guideline as it pertains to diabetic foot infections. The guideline reviews diagnostic criteria, antimicrobial therapy, and surgical therapy for osteomyelitis. Recommended antimicrobial treatment courses are 4–6 weeks. The authors present a useful treatment algorithm for patients with suspected osteomyelitis of the foot. The treatment of chronic osteomyelitis is quite difficult, especially without adequate surgical management. This guideline presents a practical table on antimicrobial therapy characterized by the extent of infection. The authors provide recommendations for long-term antimicrobial therapy, although specific antibiotic recommendations are not given. However, the guideline does not address newer antimicrobials (e.g., telavancin) or higher vancomycin trough concentrations. Long-term therapy depends on the extent and severity of infection and may be appropriate for patients with no surgical options or with persistent infection despite adequate surgical intervention.

6. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother 2003;51:1261–8.

This study focused on the microbiology and antimicrobial aspects related to osteomyelitis in patients seen at the Infections Limited clinic in Tacoma, Washington. The authors evaluated treatment outcomes and the ways in which they pertained to underlying risk factors in many patients. Four hundred fifty-four patients met the inclusion criteria for retrospective chart review. This study is one of the largest published on osteomyelitis. The authors used a Cox regression analysis and found that when *P. aeruginosa* was the initial pathogen, the recurrence risk was twice that of *S. aureus* (relative risk [RR] 2.5; 95% confidence interval [CI], 1.3–4.7; p=0.005). The association between *P. aeruginosa* and the need for amputations was strong. Methicillin-susceptible *S. aureus* infections treated with vancomycin were twice as likely to recur compared with drugs such as ceftriaxone or cefazolin (RR 2.5; 95% CI, 1.1–5.7; p=0.03). Patients treated with either cefazolin or ceftriaxone had a similar recurrence risk. The primary isolate found in this study was MSSA, accounting for 52% of all cultures obtained. The authors included all *S. aureus* isolates in the analysis, so the recurrence rate of MRSA infections treated with vancomycin is unknown. This study indicates that osteomyelitis caused by *P. aeruginosa* is associated with a greater risk that the patient will undergo an amputation. Also noted were favorable results with both cefazolin and ceftriaxone for the treatment of osteomyelitis caused by MSSA. Of interest, this article states that ceftriaxone is commonly thought to be inferior to cefazolin and nafcillin for the treatment of MSSA because of higher MIC values. This article showed that the risk of recurrence was comparable for patients treated with any of these agents. This statement suggests that ceftriaxone is an appropriate agent to use in these cases, especially for patients with OPAT, because it is given once daily.

7. Rice DAK, Mendez-Vigo L. Daptomycin in bone and joint infections: a review of the literature. Arch Orthop Trauma Surg 2009;129:1495–504.

This article discusses the pharmacology, pharmacokinetics, efficacy, and safety of daptomycin for the treatment of bone and joint infections. Literature regarding daptomycin used in bone and joint infections was identified using a database search and is discussed in detail. Agents used to treat MRSA are reviewed, with a focus on daptomycin. Studies of both MRSA and vancomycin-resistant enterococci were included. The available studies indicate that daptomycin shows activity in the treatment of gram-positive bone and joint infections. Specifically, daptomycin appears to be an effective agent when other first-line antibiotics have failed. In addition, daptomycin is well tolerated, with few adverse effects reported. This is a useful article because of the favorable results obtained with daptomycin use in osteomyelitis. There are no controlled clinical trials evaluating daptomycin use for osteomyelitis. This literature review offers valuable information regarding the use of daptomycin in bone and joint infections.

8. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004;351:1645–54.

This is a good review article about the pathogenesis, diagnosis, and treatment of PJIs. One of the most interesting and useful aspects of this article is the review of biofilms. Biofilms are an important characteristic of PJIs because organisms living within the biofilm are generally resistant to host defense mechanisms and antimicrobial-killing effects. This article discusses the role of biofilms together with microbiologic studies. In addition, the authors discuss the role of rifampin in the treatment of PJIs associated with the drug's ability to remain bactericidal against biofilm-producing organisms. The authors present a practical table regarding antimicrobial therapy for specific organisms, including drug, usual dosage, and route. This article includes a treatment algorithm for early and hematogenous PJIs. This algorithm indicates when a prosthesis should be retained versus explanted.

9. Perlroth J, Kuo M, Tan J, Bayer AS, Miller LG. Adjunctive use of rifampin for the treatment of *Staphylococcus aureus* infections. Arch Intern Med 2008;168:805–19.

This systematic review of 101 studies evaluated in vitro, animal, and human data regarding rifampin in combination with other therapies for the treatment of *S. aureus*. The results of in vitro rifampin combinations correlated poorly with in vivo outcomes. For some studies, antagonism was seen in vitro; however, successful outcomes were noted in the in vivo animal model. In the seven studies of humans, it was evident that for osteomyelitis, glycopeptides were no more effective when combined with rifampin. However, for prosthetic device–related infections, patients had improved microbiological and clinical outcomes when rifampin was combined with another antibiotic that was effective against the infecting organism. The authors conclude

that this review shows that treatment with rifampin may be reasonable in combination with other antimicrobials for infections in which there are low cure rates and patients are not at risk of rifampin-induced toxicity, including serious drug-drug interactions.

10. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. JAMA 1998;279:1537–41.

This is the only randomized controlled trial evaluating the use of rifampin in combination with ciprofloxacin for the treatment of infected PJIs with retained prostheses. The authors undertook a 24-month pilot study of rifampin added to a primary antibiotic in 11 patients with retained orthopedic device-related gram-positive infections. Nine patients (82%) were believed to have a successful treatment outcome. The two patients whose therapy failed were later determined to have received inappropriate antimicrobials. Given these results, the authors conducted a randomized, placebo-controlled, double-blind trial in which 24 patients with staphylococcal infections of stable orthopedic devices with short symptom duration (i.e., less than 1 year) were given either ciprofloxacin-rifampin or ciprofloxacin-placebo. The placebo supplied by the manufacturer of rifampin turned body fluids orange to achieve blinding. Twelve patients were included in the ciprofloxacin-rifampin group and 12 in the ciprofloxacin-placebo group. The median duration of infection for patients in the ciprofloxacin-rifampin group was 5 days versus 4 days in the ciprofloxacin-placebo group. Patients with a hip prosthesis were treated for 3 months, and those with a knee prosthesis were treated for 6 months. All patients in the ciprofloxacin-rifampin group were cured compared with 7 of 12 (58%) patients in the ciprofloxacin-placebo group (p≤0.02). Nine patients withdrew from the study for various reasons. Seven of these patients then underwent treatment with ciprofloxacin-rifampin combinations, three of them with a reduced rifampin dose. Five of the seven patients (71%) were considered cured at the end of the study. Four of the five treatment failures in the ciprofloxacin-placebo group developed ciprofloxacin-resistant staphylococci during treatment. The authors concluded that rifampin plus ciprofloxacin successfully eradicated staphylococcal infections in retained orthopedic devices if the patient had short symptom duration. The combination of rifampin and ciprofloxacin may prevent the emergence of ciprofloxacin-resistant staphylococcal isolates. Given the relatively poor gram-positive activity of ciprofloxacin, levofloxacin or moxifloxacin could be considered instead when combined with rifampin for this indication.

11. Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, et al; IDSA. Practice guidelines for outpatient parenteral antimicrobial therapy. Clin Infect Dis 2004;38:1651–72.

Evidence-based literature for OPAT is lacking. The IDSA developed these guidelines from the collective experience of the authors and their organizations. In these guidelines, the IDSA focuses on appropriate patient selection, key elements of an OPAT program, role of the OPAT team, antimicrobial selection, monitoring, outcomes and safety, and pediatric considerations. The guidelines describe necessary assessments of patients who would benefit from OPAT and the potential to either overuse or underuse such programs. The capabilities of the patients and their caregivers are an important aspect of ensuring a successful OPAT course. The patient and/or caregiver must be able to adhere to the necessary responsibilities of the drug infusion and the catheter device, as well as the reporting and communicating of all issues related to therapy to the appropriate contact person. Each member of the OPAT team has a specific function. In general, physicians are responsible for ordering OPAT services. Nurses, pharmacists, and social workers usually arrange the OPAT services while providing proper education and follow-up instructions. The IDSA guidelines recommend that OPAT programs maintain written policies and procedures outlining the responsibilities of the team members and the ways in which to deal with issues. This guideline provides an informative table regarding the important properties of common antibiotics used in OPAT programs, including stability information. The guidelines also recommend, as part of performance improvement, that OPAT programs monitor patient safety and outcomes.

Self-Assessment Questions

1. A 45-year-old man has a wound on his left index finger that occurred 2 months ago when he hooked his finger on a fishing trip. He was seen by his primary care physician at the time and was prescribed amoxicillin/clavulanate. He completed his antibiotic therapy and now presents to the emergency department (ED) with no improvement in his finger. The physician would like to evaluate him for possible osteomyelitis. **Which one of the following would be the most definitive way to diagnose osteomyelitis?**

   A. Obtain magnetic resonance imaging (MRI) of the finger.
   B. Obtain plain radiography of the finger.
   C. Look for the presence of pus, erythema, pain, and swelling of the infected site.
   D. Attempt to probe bone on examination.

2. A 61-year-old man with a longstanding history of vascular insufficiency, diabetes mellitus, hypertension, obesity, and left great toe amputation secondary to osteomyelitis 1 year ago presents to the ED with pain, warmth, redness, and foul-smelling drainage of his right heel for about 2 weeks. On examination, there is a 3-cm x 3-cm wound on the plantar aspect of the right heel. The patient has no drug allergies. **Which one of the following is the next best step for this patient?**

   A. Obtain a wound swab.
   B. Obtain an MRI.
   C. Admit for intravenous antibiotic therapy.
   D. Administer oral ciprofloxacin and clindamycin.

3. A 64-year-old man is admitted to a community hospital for pain, redness, and swelling surrounding an ulcer on the plantar aspect of his right great toe. He has type 2 diabetes mellitus, peripheral neuropathy, and hypertension. He reports no drug allergies. He denies injury or trauma to his foot and does not have fever or chills. On admission, a methicillin-resistant *Staphylococcus aureus* (MRSA) nares screen is positive, and the patient is placed on contact isolation. Physical examination shows an edematous and erythematous right great toe with extension to the midcalf. The ulcer is 1.5 cm wide and has no drainage. Plain radiography of the right foot shows cortical destruction of the underlying bone consistent with osteomyelitis at the site of the ulcer, with no other abnormalities. The patient declines a surgical consult for possible amputation and prefers to attempt a 6-week course of antibiotic therapy. **Which one of the following regimens is most appropriate for this patient?**

   A. Amoxicillin/clavulanate.
   B. Piperacillin/tazobactam plus vancomycin.
   C. Ceftazidime.
   D. Linezolid plus levofloxacin.

Questions 4 and 5 pertain to the following case.
M.T. is a 60-year-old man who is admitted for a left lower foot infection. He states he bumped his foot about 3 weeks ago and now reports chills, fever, pain, swelling, and a foul-smelling discharge from the wound site. M.T. has hypertension and diabetes mellitus and no drug allergies. On physical examination, the physician can visualize bone at the base of the wound.

4. **Which one of the following culture specimens would provide the best information about the pathogens in M.T.'s infection?**

   A. Swab taken from the bed of the ulcer.
   B. Bone cultures taken during debridement.
   C. Two sets of blood cultures.
   D. Percutaneous needle aspiration of the infection site.

5. **Which one of the following is the best empiric antibiotic regimen for M.T.?**

   A. Vancomycin and ertapenem.
   B. Levofloxacin.
   C. Cefazolin and metronidazole.
   D. Daptomycin and piperacillin/tazobactam.

Questions 6 and 7 pertain to the following case.
J.K. is a 53-year-old woman (weight 80 kg) with MRSA osteomyelitis of her left foot. Vancomycin 1 g intravenously every 12 hours and rifampin 300 mg orally two times/day were started. The isolate has a minimum inhibitory concentration (MIC) to vancomycin of 1 mcg/mL. J.K. has a serum creatinine of 0.9 mg/dL. A vancomycin steady-state trough concentration obtained this morning is 8.3 mcg/mL. She is about to be discharged home to complete 6 weeks of therapy.

6. **Which one of the following is the best recommendation regarding J.K.'s vancomycin therapy?**

   A. Increase the dosage to 750 mg intravenously every 8 hours.
   B. Continue the current dosage of 1 g intravenously every 12 hours.

C. Increase the dosage to 1.5 g intravenously every 12 hours.

D. Decrease the dosage to 750 mg intravenously every 12 hours.

7. **In addition to J.K.'s vancomycin trough concentrations, which one of the following laboratory parameters is best to monitor closely?**

A. Basic metabolic panel.
B. Liver function tests.
C. Erythrocyte sedimentation rate and C-reactive protein.
D. Complete blood cell count.

8. A 45-year-old man presents to the hospital with a 2-day history of left knee pain that occurred very suddenly. He has been experiencing subjective fevers, pain, swelling, and limited mobility in his knee. He has gout, hypertension, and osteoarthritis. He works as a carpenter and assumed that he injured his knee while at work. After an arthroscopy and drainage of his left knee, the synovial fluid analysis shows a white blood cell count of 55 x 10^3 cells/mm^3, neutrophils 84%, and no crystals. A Gram stain is pending. **Which one of the following is the best empiric treatment for this patient?**

A. Ceftriaxone.
B. Colchicine.
C. Ceftriaxone plus vancomycin.
D. Vancomycin.

9. A patient is currently on a home regimen of ceftriaxone 1 g/day for the treatment of his septic ankle caused by *Neisseria gonorrhoeae.* After completing 2 days of therapy, he calls to report a localized rash on his abdomen and back. He states that it is very uncomfortable. **After discontinuing ceftriaxone, which one of the following agents is the best option for this patient?**

A. Cefotaxime.
B. Levofloxacin.
C. Cefixime.
D. Doxycycline.

10. A 42-year-old man has an infection of his total knee arthroplasty. He underwent irrigation and debridement of the infected joint with retention of the prosthesis. Intraoperative cultures have grown methicillin-susceptible *S. aureus* (MSSA). He has no drug allergies; thus, he will be discharged home on outpatient parenteral antibiotic therapy (OPAT) for his infection. **Which one of the following is the best treatment option for this patient?**

A. Nafcillin.

B. Nafcillin plus rifampin.
C. Cefazolin.
D. Vancomycin plus rifampin.

11. A study will be conducted comparing outcomes in patients with MSSA joint infections. Patients with MSSA culture proven infected knee or hip prostheses will be randomized to receive either nafcillin or cefazolin for 6 weeks. The investigators would like to enroll 50 patients in each group. They will use the proportion of patients who have a clinical cure at the end of 6 weeks as their primary end point. Which one of the following is the best statistical test for this type of investigation?

A. Paired t-test
B. Student t-test
C. Chi-square test.
D. Analysis of variance.

12. A patient has an infected total hip arthroplasty with retained prosthesis and intraoperative cultures positive for MRSA. The organism is susceptible to clindamycin, vancomycin, co-trimoxazole, doxycycline, levofloxacin, rifampin, and linezolid and resistant to oxacillin and erythromycin. **Which one of the following suppressive regimens is the best option for this patient?**

A. Co-trimoxazole plus rifampin.
B. Linezolid plus rifampin.
C. Doxycycline.
D. Levofloxacin.

13. A patient is being treated for a septic arthritis involving his knee. After a closed-needle aspiration, cultures have grown *E. coli* susceptible to cefazolin, ceftriaxone, ampicillin/sulbactam, co-trimoxazole, ciprofloxacin, and levofloxacin and resistant to ampicillin. **Which one of the following is the best treatment option for this patient?**

A. Amoxicillin/clavulanate for 3 weeks.
B. Co-trimoxazole for 1 week.
C. Ceftriaxone for 3 weeks.
D. Ciprofloxacin for 6 weeks.

14. An 84-year-old woman has a total hip arthroplasty for severe osteoarthritis. Two weeks later she develops a prosthetic hip infection. The intraoperative cultures have grown MSSA, and her prosthesis is considered stable. **Which one of the following is the best treatment option for this patient?**

A. Cefazolin plus rifampin for 6 weeks followed by oral suppression.
B. Debridement, irrigation, and retention of joint followed by intravenous antibiotics.

C. A two-stage revision followed by 4 weeks of intravenous antibiotics.

D. Nafcillin plus rifampin for 4 weeks followed by debridement and irrigation of the joint.

15. A 56-year-old man (height 6′1″, weight 94 kg) develops ankle septic arthritis. The initial synovial fluid Gram stain shows gram-negative rods. He has a history of diabetic nephropathy and has a current creatinine of 2.2 mg/dL. **Which one of the following is the best empiric treatment regimen for this patient?**

A. Cefazolin 2 g intravenously every 12 hours.

B. Meropenem 1 g intravenously every 8 hours.

C. Ertapenem 1 g intravenously daily.

D. Cefepime 2 g intravenously every 12 hours.

16. A 65-year-old woman with an MSSA infection of her right prosthetic knee underwent a two-stage revision. She would like to complete her antibiotic therapy at home. She lives alone and has severe arthritis of her hands. **Which one of the following is the best option for this patient?**

A. Nafcillin 2 g every 4 hours given by 30-minute infusions.

B. Cefazolin 2 g every 8 hours given by 10-minute push.

C. Vancomycin 1 g every 12 hours given by 60-minute infusion.

D. Nafcillin 12 g given by continuous-infusion pump.

17. A 72-year-old man is undergoing treatment for left heel osteomyelitis. He is on empiric therapy with meropenem and daptomycin 6 mg/kg intravenously daily. He has a documented allergy to vancomycin (rash) and peripheral vascular disease, diabetes mellitus, hypertension, and dyslipidemia. The patient is receiving his antibiotics through OPAT. His medical conditions are controlled with insulin, lisinopril, and simvastatin. His baseline creatine kinase was 35 units/L; today, his creatine kinase is 247 units/L. The patient reports a pain score of 1. **Which one of the following is the best option for this patient?**

A. Discontinue daptomycin and start vancomycin.

B. Decrease daptomycin dose and hold simvastatin.

C. Continue daptomycin and hold simvastatin.

D. Decrease daptomycin dose.

18. A 24-year-old man presents to the ED with a swollen, painful left knee. He states that for the past 2 days, he has had fever and shaking chills. He also reports a slightly itchy rash on his abdomen and arms. Of note, his rash consists of raised, pink papules. He has multiple sexual partners. He has no chronic medical conditions and takes no drugs. He developed a rash to penicillin years ago. **Which one of the following is the best option for this patient?**

A. Admit to the hospital and begin ceftriaxone.

B. Discharge with cefixime orally.

C. Discharge with levofloxacin orally.

D. Admit to the hospital and begin doxycycline.

19. A 53-year-old man has received a diagnosis of a septic joint caused by *Klebsiella pneumoniae.* The organism is susceptible to ampicillin/sulbactam, piperacillin/tazobactam, ceftriaxone, levofloxacin, ciprofloxacin, and gentamicin and resistant to ampicillin and cefazolin. **Which one of the following is the best outpatient regimen for this patient?**

A. Piperacillin/tazobactam 3.375 g intravenously every 6 hours by infusion pump.

B. Ceftriaxone 2 g intravenously once daily by intravenous push.

C. Cefpodoxime 400 mg orally two times/day.

D. Ciprofloxacin 750 mg orally two times/day.

20. A 40-year-old man is undergoing treatment for a prosthetic knee infection caused by MRSA. The MRSA is susceptible to vancomycin, co-trimoxazole, doxycycline, levofloxacin, and linezolid and resistant to oxacillin, clindamycin, and erythromycin. He has completed a 6-week course of vancomycin and rifampin. His physician would like to start chronic suppressive therapy. **Which one of the following is the best suppressive regimen for this patient?**

A. Levofloxacin plus rifampin for 3 months.

B. Co-trimoxazole for 6 months.

C. Doxycycline plus rifampin for 6 months.

D. Doxycycline for 3 months.

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